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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,089	01/28/2008	Catherine Lofton-Day	47675-066US0	9399

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EXAMINER	
BAUSCH, SARAE L	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,089	LOFTON-DAY ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-22 and 24* is/are pending in the application.

4a) Of the above claim(s) *4,6,7 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 8-21, 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 03/16/2010. The amendment to the claims mailed 03/16/2010 has been entered

Election/Restrictions

2. Applicant's election with traverse of group I and the combination of ALX4 and TPEF in the reply filed on 03/16/2010 is acknowledged. The traversal is on the ground(s) that SEQ ID NO 7, 8, 15, 16 correspond to SEQ ID NO 2 and SEQ ID NO 9, 10, 17-18 correspond to SEQ ID NO 3 which is found persuasive and the combination of SEQ ID NO 2, 3, 7-10 and 15-18 is being examined. Applicant assert that one member ALX4 of the elected combination ALX4 and TPEF be included in the elected group as searching this claim is not a burden and the claims do not require APC, p16INK4a, DAPK, TIMP3 therefore subject matter of the claims of groups I and II are now liked as they share a common special technical feature of the bisulfite converted sequences SEQ ID NO 7-10, 15-18. This is not found persuasive because search burden is not a requirement for unity of invention in a national stage application. Furthermore the common special technical feature of groups I and II, with the newly amended claims is not SEQ ID NO 7-10 and 15-18 as claims 1, 4 or 5 do not require these sequences or combination. For example claim 4 only requires the ALX4 gene therefore does not require any combination of bisulfite converted sequences. Additionally claims 1 and 5 are not limited to detecting or analyzing bisulfite converted sequences of SEQ ID NO 7-10 and 15-18. The special technical feature linking the inventions is merely methylation of ALX4 gene, which was known in the art as Yan

(2000, cited on IDS) teaches methylated ALX4 gene and therefore not a special technical feature of the prior art.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4, 6, 7, and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03/16/2010.

4. It is noted that claim 4 is withdrawn as it is drawn to only ALX4 however claim 5, which requires the combination of ALX4 and TPEF is being examined. Any claim that depends from claim 4 which require does not require the combination of ALX4 and TPEF is withdrawn. The claims are being examined for the combination of ALX4 and TPEF.

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. There are no sequence identifiers for the sequences listed throughout the specification. Applicant is required to thoroughly review the specification and comply with all sequence rules. For example, the following sequences in the specification do not have sequence identifiers: page 35, 37, 44. For any response to this office action to fully responsive, applicants are required to comply with sequence rules.

Specification

6. The disclosure is objected to because of the following informalities: the specification spacing between words in the specification needs to be corrected. Applicant is required to review the entire specification and correct any spacing errors between letters and words. For example pg. 23, 25, 27.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5, 8-21, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 5 are indefinite because the claims do not recite a clear nexus between the preamble of the claim and the process steps of the claims. The preamble states a method for detection of a colorectal cell proliferative disorders. The positive active steps of the claims are drawn to determining a CpG methylation status of two genes and deducing based on methylation status the presence or absence of a colorectal cell proliferative disorder or metastasis. The claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The preamble does not require detection of the absence of a colorectal cell proliferative disorder or metastasis and therefore it is unclear if the claims are drawn merely

to detection of colorectal cell proliferative disorders, or drawn to detecting both the presence or absence of colorectal cell proliferative disorder and metastasis.

Claim Rejections - 35 USC § 112/Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 5, 8-21, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for increased likihood of colorectal cancer in a human patient comprising:

(i) obtaining a biological sample comprising colorectal cells from the patient,

(ii) determining a methylation level of ALX4 and TPEF in the sample, and

(iii) comparing the methylation level of ALX4 and TPEF in the sample with the methylation level in normal colorectal cells, wherein a higher degree of methylation in the sample compared to normal colorectal cells indicates an increased likihood of colorectal cancer, does not reasonably provide enablement for the claims as written. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8

USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

The claims are draw to a method of detecting colorectal cell proliferative disorders comprising determining CpG methylation status of ALX4 and TPEF in a subject and deducing based on the methylation status the presence, absence of a colorectal cell proliferative disorder or metastasis. Dependent claims limit the sequences detected by hybridization or PCR as well as limit the type of biological sample.

The claims therefore are broadly drawn to detecting any colorectal cell proliferative disorder in any subject, human or non-human by detection of any difference in methylated and non-methylated CpG dinucleotides of ALX4 and TPEF in any sample. When the claims are read in light of the specification, the specification does not provide predictable guidance and the art, as presented below, that such correlations are unpredictable.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification asserts that the invention provides a method of determining based on at least distinguishing the methylation state of a gene panel for detection of colon cell proliferative disorders with high sensitivity and specificity. The specification asserts that the use of bisulfite technique with one or more methylation assay determines the methylation status of CpG dinucleotides sequences of at least two genes, ALX4 and TPEF (see pg. 13) However, the instant specification has not provided any guidance as to which CpG dinucleotides are associated with colorectal cell proliferation. The instant specification has not provided any guidance as to which methylation states must be detected to be associated with each particular colorectal cell proliferative disorder. The instant specification has not provided any guidance as to which differences in methylation are associated with presence or absence of colorectal cell proliferative disorders or metastases.

The specification provides figures; however, none of these figures are drawn to CpG sites within ALX4 and TPEF. Specifically these figures disclose degree of methylation but not methylation status of CpG sites. Therefore the drawings in the instant application do not provide guidance to the detection of colorectal cell proliferative disorder by determining any CpG methylation status of ALX4 or TPEF.

The instant specification does not provide a definition for the term "subject". As such "subject" can be considered any species including dog, cat, and human. The instant specification has not provided guidance to determine if a correlation of methylation status in one species can be extrapolated to any other species. Further the art teaches that such methylation status is species dependent.

The instant specification discloses various methodologies to detect CpG methylation status (p. 12-13 and p. 15-17). However, the specification does not disclose the determination of colorectal cell disorder by detection of CpG methylation status in ALX4 and TPEF in any of these various methodologies. The specification merely provides analysis of increased methylation within the ALX4 and TPEF gene is associated with increased likihood of colorectal cancer.

The specification asserts that the present invention provides the use of a bisulfite technique for determination of the methylation status of CpG dinucleotides sequences within genomic sequences and/or regulatory region of ALX4 and TPEF and that such determination has diagnostic and prognostic utility (p. 13). However, the specification has not provided any guidance or data for the association of the methylation status of a specific CpG dinucleotides sequences within genomic sequences of ALX4 and TPEF and colorectal proliferative disease. The art, as described below, teaches that such associations are unpredictable and do no make for good cancer diagnostic markers.

The specification asserts that the instant invention is based upon the analysis of methylation status of at least one CpG position of ALX4 and or its regulatory sequence in addition to TPEF (see pg. 14, lines 15-23). The specification asserts that hypermethylation within ALX4 and TPEF and/or their regulatory sequence in the form of a panel enable the detection of varying degrees of probability of the presence of colon cell proliferative disorders and or metastases thereof. However, the specification has not provided any guidance or data for the association of the methylation status of CpG of any dinucleotides sequences within genomic sequences and/or regulatory sequence of ALX4 and TPEF and any type of colorectal

proliferative disease.

The specification provides examples. Example 1 is based upon differential methylation of a genomic sequence of ALX4 in DNA from healthy colon, adenomas, and colon adenocarcinoma tissue (p. 32 lines 1-5). The instant specification provides method steps to AP-PCR (p. 37-38). The specification provides analysis of methylation of TPEF and ALX4 which exhibited a high frequency of methylation in primary colon cancer (see table 3). It is noted that although example 1 provides analysis and statistically significant results for the association of high frequency of methylation in colon cancer compared to normal of the genes TPEF and ALX4 this does not teach how to determine any presence or absence of colorectal cell proliferative disorder or metastases based on "a", one CpG methylation status within any portion of the gene of TPEF and ALX4 in any subject, human or non human.

In summary, the claims are drawn to detection of any colorectal cell proliferative disorder or distinguishing between any colorectal cell proliferative disorders in any subject, however, the specification does not provide a predictable correlation of any methylation status of SEQ ID NO. 6 or 21 to such a correlation.

The predictability or unpredictability of the art and degree of experimentation

Ehrlich et al. (2002 Oncogene Vol 21 p. 5400) teaches that hypomethylation and hypermethylation of DNA are relative terms and demote less or more methylation than in some standard DNA (p. 5400 last paragraph). Ehrlich et al. teaches that there are considerable differences in the amounts and distribution of DNA methylation among different vertebrate tissues because DNA methylation is not only species-specific but also tissue-specific (p. 5400

last paragraph). Therefore the association in one species of CpG islands to cancer type cannot be extrapolated to any species predictably. Because the distribution of DNA methylation varies between species it is not predictable that the same methylation status differences observed in one species is correlative in another species.

The art teaches that there is an unpredictability based on reference comparison and sample type.

Ehrlich et al. teaches that therefore unless the studied tumor DNA is being compared to a relatively pure population of cells which is know to be the cell of origin of the tumor it is best to use DNA from a variety of normal tissues as the control (p. 5401 1st column 1st paragraph). Ehrlich et al. teaches that also in identifying cancer-specific differences in genome methylation that the studied cells should be uncultured cell populations because of the frequent changes in DNA methylation that occur upon cell culture (p. 5401 1st paragraph). Therefore Ehrlich et al. teaches that not all cell populations (e.g. samples) have the same correlation to methylation.

Ehrlich et al. teaches that how early DNA hypomethylation can be detected during tumorigenesis may depend on the type of tumor as well as the individual tumor sample (p. 5401 2nd column 1st paragraph). Therefore the art teaches that there is unpredictability in diagnosing cancer in any sample type and such correlations are sample specific.

The art teaches that the correlation of methylation statues to cancer is unpredictable. Ehrlich et al. teaches that a correlation to cancer would not have been found in only one CpG island and one normal tissue type was used.

Ehrlich et al. teaches that hypermethylation of 12 CpG islands at the 5' end of tumor suppressor genes was investigated in a methylation sensitive PCR of 600 cancers (p. 5403 1st

paragraph). Ehrlich et al. teaches that cancer-associated hypermethylation was found in most tumors of a given type in at least a few of the CpG islands however the pattern of which CpG islands are hypermethylation varied with the kind of cancer (p 5403 1st paragraph). Ehrlich et al. teaches that this hypomethylation probably would have been missed if the analysis for methylation had not been quantitative and had not included a variety of normal tissue DNAs (p. 5408 1st full paragraph last sentence).

The art teaches that generally methylation is not used for diagnostic markers.

Cottrell (clinical Biochemistry 2004 Vol. 37 p. 595) teaches that because methylation-based markers are not routinely used in clinical labs, the methodology has not been fully optimized, validated, and standardized. Cottrell et al. teaches that most of the methylation methods rely on bisulfite treatment protocol which must meet strict requirements for consistency and performance (p. 601 1st column 2nd full paragraph). Cottrell et al. teaches that in order to discover optimal markers and crease successful assays, there will need to be clearly defined clinical questions, sample sets, and methodologies coupled with the current methylation technologies (p. 601 1st column last paragraph).

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to detect the presence or absence of any colorectal proliferative disorder or metastases by determining a CpG methylation status of ALX4 and TPEF in any animal. The specification does not provide any data to the association of methylation status of ALX4 and TPEF in any subject to colorectal proliferative disorder. The specification does provide guidance that a higher degree of methylation of ALX4 and TPEF compared to normal colon cells is associated with increased risk of colon cancer however this does provide any guidance to determine the presence or absence of

any type of colorectal proliferative disorder or metastases in any subject, human or non-human. The art teaches that methylation markers are not used as diagnostic markers because of the unpredictability in determining methylation status. The art teaches that methylation is species and tissue dependent. The art teaches that such correlations can not be extrapolated between cancer types. The art teaches that multiple reference samples must be used and multiple CpG islands.

The skilled artisan, therefore, would have to perform undue experimentation to determine the correlation of colorectal cell proliferative disorder and metastases in any subject based on methylation status of ALX4 and TPEF.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written. The skilled artisan would have to determine which CpG islands in ALX4 and TPEF were correlative to colorectal cell proliferative disorders. The skilled artisan would have to test methylation status in many species without an expectation of a predictable success in of detection in each species type. The skilled artisan would have to test multiple sample types and CpG islands in multiple types of colorectal cell proliferative disorders. The skilled artisan would have to detect multiple reference samples.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide a predictable correlation of any CpG methylation status change in SEQ ID NO. 6 or 21 in any subject to detect colorectal cell proliferative disorder or to distinguish between colorectal cell proliferative disorders. Further, the art teaches that this correlation would be different depending on the number of CpG islands tested and the reference samples which were compared.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Sarae Bausch/
Primary Examiner, Art Unit 1634